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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,437	11/16/2001	David Botstein	P2730P1C49	2360

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EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 04/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,437	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124,129-131 and 135-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124,129-131 and 135-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The rejection under 35 USC 112, second paragraph, is withdrawn in view of the cancellation of the claim.

The rejection under 335 USC 112, first paragraph, is withdrawn upon further consideration and is replaced with new rejections here.

The rejection under 35 USC 102(a) is withdrawn in view of the amendment to the claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 124, 129-131 and 135-138 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The instant claims are drawn to a nucleic acid comprising SEQ ID NO:32 or the full-length coding sequence of the cDNA of ATCC 209790. The previous Office action indicated that this nucleic acid was enabled because it is amplified in squamous cell-type lung carcinomas, with 5/11 SqCCa showing a $\Delta Ct > 1.0$. However, upon further reconsideration and finding of new related art, it has been determined that the invention does not have utility. The reasons is that the significance of the ΔCt was based on the use of normal controls of genomic DNA from human blood (pages 547-548) and did not take into account controls for aneuploidy of the tumor tissue used. At page 545, Ct is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification indicates that Ct is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." The Examiner is unable to find, either in the specification or in the art, an explanation of how Ct values are calculated, nor what the significance of such are. It is

noted that the ΔCt values at page 550 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.63), and (b) that only one sample, "LT19", gave values that were consistently at least 2. It is not clear how measurements of hundredths of a PCR cycle can be made, nor what the significance of a difference of 1 or 2 PCR cycles would be. Given the paucity of information, the data do not support the implicit conclusion of the specification that PRO290 shows a positive correlation with lung SqCCa or other cancer, much less that the levels of PRO290 would be diagnostic of such. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not supported by analysis of mRNA or protein expression, for example. Thus, the data do not support the implicit assertion that PRO290 can be used as a cancer diagnostic.

While the nucleic acid showed slight amplification in tumor cells, particularly lung squamous cell carcinomas, compared to normal tissue, this does not support a diagnostic use of the nucleic acid for detection of cancerous tissue. Hittelman (Ann. NY Acad. Sci., 952:1, 2001) showed that chromosomal polysomy occurred with a much greater likelihood in cancerous compared to adjacent normal epithelium (p. 6, third paragraph). That means an increased copy number for PRO290 in lung tumors tested was less likely due to an increase unique to PRO290 DNA, but rather due to a more general phenomenon of polysomy of the DNA in epithelial cancers. Additionally, it was also found that, "[T]he presence or absence of squamous metaplasia at biopsy site does not necessarily correlate with the degree of underlying genomic instability," (p. 8, second paragraph). Further, in individuals who had stopped smoking, chromosomal instability was still evident despite the decrease risk of lung cancer, drawing the conclusion that "individuals are differentially sensitive to carcinogenic insult," (p. 8, end of third paragraph). To further complicate the matter of the association of chromosomal polyploidy with cancer, Jeanfaivre et al. (Bulletin du Cancer, 84(6):597, 1997, abstract) found that in 61 cases of squamous cell lung carcinoma studied, "DNA content classified as DNA-diploid and DNA-aneuploid is not a prognostic factor for survival." Because of the above considerations, significant further research would have been required of the skilled artisan to determine whether

PRO290 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial or specific.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 124, 129-131 and 135-138 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

It would require significant further experimentation to be able to use the claimed polynucleotide because no particular function or specifically associated disease has been determined for the polynucleotide of SEQ ID NO:32, and there is no disclosed definite function supported by the prior art. No function can be reasonably assigned based on its homology to another polynucleotide(s). Using the claimed polynucleotide would require undue experimentation.

Conclusion

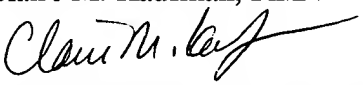
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 9:00AM to 3:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (571) 272-0829.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Claire M. Kaufman, Ph.D.



Patent Examiner, Art Unit 1646

April 18, 2005